REMARKS

Provisional Double Patenting Rejection of Claims 10, 11 and 18

Claims 10, 11 and 18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting "as being unpatentable over claim 1 of copending Application No. 10/686,943" (Office Action, page 3). The Examiner states that "[i]t should be noted that Applicant did not traverse this rejection in his response" (Office Action, page 3).

Applicants note, however, that an indication of allowable subject matter has not been made in the instant application or in copending Application No. 10/686,943. Therefore, it is not possible for Applicants to comment on whether the claims in a patent that issues from the instant Application would be obvious over the claims in a patent that issues from copending Application No. 10/686,943 until an indication of allowable subject matter has been made. Because this is a provisional obviousness-type double patenting rejection, Applicants will not address the rejection until an indication of allowable subject matter has been made. Applicants decision not to respond to the double patenting rejection is not an admission that the claims of the instant application are obvious over one or more claims of copending Application No. 10/686,943.

Rejection of Claims 10-13 and 17-21 under 35 U.S.C. §103(a)

Claims 10-13 and 17-21 are rejected under 35 U.S.C. §103(a) "as being unpatentable over McMichael et al. (WO 98/56919) and Kazanji et al. (International Journal of Cancer, 1997, Vol. 71, pages 300-307 – IDS filed on 3-21-2002)" (Office Action, page 4). The Examiner states that "[c]ontrary to Applicant's assertion, Kazanji et al. explicitly disclose that WKY rats were 'primed with Ad5-HTLV-I-*env* or naked DNA plasmids containing the HTLV-I-*env gp46* gene. . . and boosted with Ad5 containing the HTLV-I-*env gp46* gene. . .'" and that "Kazanji et al. disclose the efficacy of adenovirus vectors as boosting compositions" (Office Action, page 5). The Examiner concludes that "one would have been motivated to use the adenovirus vectors disclosed by Kazanji *et al.* in the compositions and methods disclosed by McMichael *et al.* in order to take advantage of the ability of the adenovirus vectors to be orally administered and to be cheaply made" and that "[o]ne would have had a reasonable expectation of success as

adenovirus vectors have been successfully used in other vaccine compositions and in prime-boost methodologies" (Office Action, pages 6-7).

Applicants respectfully disagree. The Examiner has relied upon a portion of a sentence in the abstract of Kazanji *et al.* to support the conclusion that "Kazanji et al. disclose the administration of naked DNA plasmids containing the HTLV-I-*env* gene as the 'primer' and the administration of Ad5 containing the HTLV-I-*env gp46* gene as the 'booster'" (Office Action, page 7). However, Kazanji *et al.* do not disclose such a regimen.

Kazanji *et al.* compared immunization regimens against HTLV-1 by inserting the complete HTLV-1-*env* gene in a recombinant adenovirus (Ad5-HTLV-I-*env*), a naked DNA plasmid (pMLP-HTLV-I-*env*) and a recombinant vaccinia virus (WR-SFB*5env*). Kazanji *et al.* summarize the specific immunization regimens or vaccination protocols employed in their experiments in Tables 1A, 1B and 1C (Kazanji *et al.*, page 301). The particular vaccination protocols using Ad5-HTLV-I-*env* are summarized in Table 1A. Notably, Kazanji *et al.* state that the "initial aim of the experiment was to ***compare*** immunization with the complete HTLV-I-*env* gene inserted into the adenovirus vector (Ad5-HTLV-I-*env*) ***or*** in a naked DNA plasmid (pMLP-HTLV-I-*env*)" (Kazanji *et al.*, sentence bridging pages 302 and 303; emphasis added), as opposed to using an adenovirus vector and a DNA plasmid together in the same vaccination protocol.

Accordingly, although Kazanji *et al.* employed adenovirus vector as a boosting composition in a ***homologous*** prime-boost vaccination regimen, Kazanji *et al.* do not teach or suggest using adenovirus as a boosting composition in a heterologous prime-boost method. In Tables 1A, 1B and 1C, it is clear that three ***homologous*** prime-boost vaccinations were carried out using either Ad5-HTLV-I-*env* (Table 1A), pMLP-HTLV-I-*IV* (Table 1B) ***or*** WR-SFB*5env* (Table 1C) and that heterologous prime-boost regimens were carried out using Ad5-HTLV-I-*env* (Table 1A) or pMLP-HTLV-I-*IV* (Table 1B) as a prime, and recombinant gp46 protein (Baculo.rgp46) as a boost. However, Kazanji *et al.* did not perform a heterologous prime-boost regimen using a DNA plasmid prime and an adenovirus vector boost.

Moreover, Kazanji *et al.* teach away from using a heterologous prime-boost regimen by disclosing that only WKY-vaccinated rats that were subjected to a homologous prime-boost vaccination protocol using either 1) an Ad5-HTLV-I-*env* prime and an Ad5-HTLV-I-*gp46* boost,

or 2) a pMLP-HTLV-I-*IV* prime and a pMLP-HTLV-I-*gp46* boost were protected from subsequent HTLV-1 infection, as evidenced by lack of detectable provirus. Specifically, Kazanji *et al.* teach that "provirus was detected in all the rates except 3" (Kazanji *et al.*, page 303, last paragraph). Of the three rats in which provirus was not detected, "2 of these rats had been primed with Ad5-HTLV-I-*env* and boosted with Ad5-HTLV-I-*gp46*; and the third had been immunized with pMLP-HTLV-I-*env* and boosted with pMLP-HTLV-I-*gp46*" (Kazanji *et al.*, page 303, last paragraph). Applicants further direct the Examiner's attention to the data in TABLE II of Kazanji *et al.*, which show that all of the rats that were subjected to a heterologous prime-boost vaccination protocol displayed detectable levels of provirus upon subsequent challenge (Kazanji *et al.*, page 306). Thus, the data in TABLE II suggest that homologous prime-boost regimes are preferable to heterologous prime-boost regimes for inducing protection. Furthermore, the teachings of Kazanji *et al.* suggest that one of skill in the art should practice a ***homologous*** prime-boost method using an adenovirus vector in order to take advantage of the suitability of adenovirus for oral administration, as opposed to a heterologous prime-boost method using a recombinant protein, which is not as suitable for oral administration.

In contrast to the teachings of Kazanji *et al.*, McMichael *et al.* disclose heterologous prime-boost methods of generating a CD8+ T cell response against a target antigen comprising administering a priming composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, together with a carrier, and a boosting composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, including at least one CD8+ T cell epitope which is the same as a CD8+ T cell epitope of the priming composition, wherein the source of CD8+ T cell epitopes is a non-replicating or replication-impaired recombinant poxvirus vector with the proviso that if the source of epitopes in the priming composition is a viral vector, the viral vector of the boosting composition is derived from a different virus (McMichael *et al.*, page 10, lines 6-24). As the Examiner notes, McMichael *et al.* do not disclose "the use of boosting compositions comprising non-replicating or replication impaired adenovirus vectors" (Office Action, page 7).

The combined teachings of Kazanji *et al.* and McMichael *et al.* would not motivate one of skill in the art to substitute the non-replicating or replication-impaired recombinant poxvirus vector of McMichael *et al.* with the adenoviral vector of Kazanji *et al.* to practice Applicants'

claimed heterologous prime-boost method of inducing a CD8+ T cell immune response to an antigen in an individual because Kazanji *et al.* teach away from using an adenovirus vector in a heterologous prime-boost method. Furthermore, Kazanji *et al.* provide no motivation whatsoever to use an adenovirus vector as a boosting composition in a heterologous prime-boost method. There is no teaching or suggestion in the McMichael *et al.* reference or the Kazanji *et al.* reference as a whole to suggest the desirability, and thus obviousness, of using the adenovirus vector of Kazanji *et al.* in the heterologous prime boost method of McMichael *et al.*

Clearly, Applicants' invention, as set forth in Claims 10-13 and 17-21, is not rendered obvious by the combined teachings of McMichael *et al.* and Kazanji *et al.*

Rejection of Claims 10-13 and 17-21 under 35 U.S.C. §103(a)

Claims 10-13 and 17-21 are rejected under 35 U.S.C. §103(a) "as being unpatentable over McMichael et al. (WO 98/56919) and Natuk et al., 1993, AIDS Research and Human Retroviruses, Vol. 9 No 5, pages 395-404 – IDS filed on 3-21-2002)" (Office Action, page 7). According to the Examiner, Natuk *et al.* disclose that "human adenoviruses possess significant advantages as vectors for recombinant vaccines including a strong safety record and multiple serotypes that can be exploited as vectors for booster immunizations" (Office Action, pages 8-9). The Examiner concludes that "it would have been obvious for one of ordinary skill in the art at the time the invention was made to use the adenovirus vectors disclosed by Natuk et al. in the compositions and methods disclosed by McMichael et al. in order to take advantage of the safety and versatility associated with adenovirus vectors" and "it would have been equally obvious to render the adenovirus vectors replication-deficient in order to take advantage of their increased safety (as disclosed by McMichael et al.)" (Office Action, page 9).

Applicants respectfully disagree. Natuk *et al.* clearly teach away from using a replication-deficient adenoviral vector in a method of inducing a CD8+ T cell response against an antigen in an individual. For example, Natuk *et al.* tested "[r]ecombinant human adenovirus (Ad) type 4-, 5-, and 7-vectored vaccines expressing either the HIV *env* or *gag*-protease genes" for immunogenicity in chimpanzees (Natuk *et al.*, abstract). Natuk *et al.* teach a first phase of the vaccination protocol which consisted of "a primary and two booster immunizations with Ad-HIVs by the oral route of administration, followed by a single booster immunization with Gag

and/or Env subunit vaccines" (Natuk *et al.*, abstract). Natuk *et al.* teach that a "primary purpose of this study was to evaluate the capacity of Ad-HIV recombinant viruses ***to replicate*** and induce humoral, secretory, and cellular immune responses in the chimpanzee, the only animal known to be permissive to enteric replication by the Ad4 and Ad7 vectors" (Natuk *et al.*, page 401, right column under "DISCUSSION"; emphasis added), indicating that the authors recognized viral replication to be an important factor for inducing an immune response (e.g., a cellular immune response) in vivo.

In addition, although Natuk *et al.* discuss the possibility that the adenoviral vectors are attenuated, which is different than replication-deficient, Natuk *et al.* clearly state that a "key issue regarding the utility of adenovirus vectors as vaccines is whether recombinant adenovirus ***replication*** will occur in individuals that possess preexisting immunity to the vector and whether the amount of recombinant antigen expression resulting from such infections is sufficient to stimulate strong immune responses to the foreign antigen" (Natuk *et al.*, page 402, left column; emphasis added). Natuk *et al.* clearly teach that the expression of a high level of recombinant antigen, which depends upon adenoviral replication, is critical for the induction of an effective immune response. Accordingly, Natuk *et al.* direct one of skill in the art to employ a replicating adenovirus in a method of inducing a CD8+ T cell response against an antigen in an individual in order to maximize expression of the antigen, as opposed to using a replication-deficient adenoviral vector, which expresses less antigen and therefore would be expected to be less effective for inducing an immune response against the antigen.

As discussed above, McMichael *et al.* disclose heterologous prime-boost methods of generating a CD8+ T cell response against a target antigen comprising administering a priming composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, together with a carrier, and a boosting composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, including at least one CD8+ T cell epitope which is the same as a CD8+ T cell epitope of the priming composition, wherein the source of CD8+ T cell epitopes is a non-replicating or replication-impaired recombinant poxvirus vector with the proviso that if the source of epitopes in the priming composition is a viral vector, the viral vector of the boosting composition is derived from a different virus (McMichael *et al.*, page 10, lines 6-24).

In direct contrast to the teachings of Natuk *et al.*, McMichael *et al.* reported that "the greatest immunogenicity and protective efficiency is surprisingly observed with non-replicating [poxvirus] vectors" (McMichael *et al.*, page 10, lines 1-3). Therefore, there is no motivation to combine the teachings of Natuk *et al.* and McMichael *et al.* because McMichael *et al.* teach the use of non-replicating or replication-impaired recombinant poxvirus vectors in methods for inducing an immune response, while Natuk *et al.* teach away from using non-replicating or replication-impaired adenoviral vectors by suggesting that efficiently replicating adenoviruses that express a large amount of antigen are important for inducing an effective immune response against the antigen.

Although McMichael *et al.* teach that non-replicating vectors "have an added advantage for vaccination in that they are generally safer for use in humans than replicating vectors" (McMichael *et al.*, page 10, lines 3-5), Natuk *et al.* clearly teach that replicating adenoviruses can also be used safely in humans by disclosing that "Ad4 and Ad7 vaccines administered by the oral route to military personnel have established an ***enviable safety record*** over two decades of use" (page 402, left column; emphasis added). Thus, even if one of skill in the art were to make the improper combination, the combined teachings of Natuk *et al.* and McMichael *et al.* would not motivate one of skill in the art to modify a replicating adenovirus in an attempt to render the virus safe because replicating adenoviruses already have a well-established strong safety record.

Thus, the combined teachings of McMichael *et al.* and Natuk *et al.* do not render Applicants' claimed invention obvious.

Fifth Supplemental Information Disclosure Statement

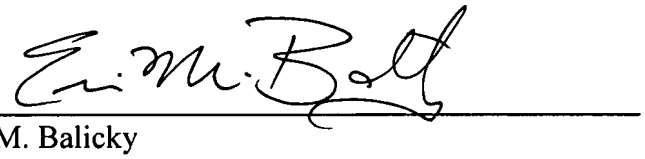
A Fifth Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

Eric M. Balicky
Registration No. 57,020
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

Date: August 30, 2007